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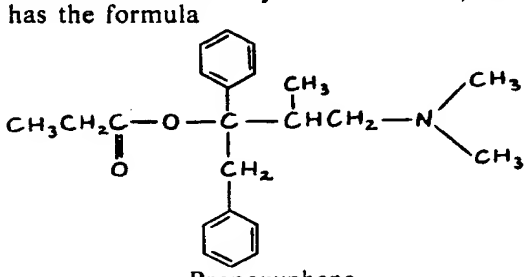
(19)

(54) ANALGESIC COMPOSITIONS COMPRISING DEXTROPROPOXYPHENE AND BENZODIAZEPINES

(71) I, FRANK MILAN BERGER of 190 East 72nd Street, New York, United States of America, a citizen of the United States of America, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to analgesic compositions, to pharmaceutical compositions containing them and to their use in relieving pain.

Propoxyphene, 4 - dimethylamino - 3-methyl - 1,2 - diphenylpropionooxybutane, is related structurally to methadone, and has the formula



Propoxyphene

The compound exists as four stereoisomers. The less soluble diastereoisomer is designated as the α-isomer, and the more soluble as the β-isomer. The α, d, l- and α,-d-diastereoisomers have marked analgesic activity. The α,-l-diastereoisomer has no analgesic action, but it has antitussive activity. The β-diastereoisomers are substantially inactive. *The United States Dispensatory,* 26th Edition, page 963, indicates that the α, dextro isomer, α, d-propoxyphene hydrochloride, is as effective in humans as codeine phosphate in relieving pain. On the other hand, the α,-d,l-racemate has about one-half the analgesic potency of codeine, due no doubt to the presence in an amount of 50% by weight of the analgesically-inactive α, laevo isomer. Regarding the α, laevo isomer, *The United States Dispensatory* states that, in contrast to propoxyphene, l-propoxyphene has therapeutically useful antitussive activity but no analgesic action.

α,-*d*-propoxyphene has little, if any, addicting liability, and is used to provide relief in mild to moderate pain, whether acute, chronic, or recurrent. It tends to produce fewer gastrointestinal side effects than codeine, but it is not sufficiently potent to relieve severe pain, and it is of little utility as an antitussive. Several formulations of α, d-propoxyphene hydrochloride are available commercially.

Goodman and Gilman, *The Pharmaceutical Basis of Therapeutics,* 3rd Edition, indicate that α, *d*-propoxyphene produces analgesia by acting on the central nervous system. Oral doses of the order of 65 to 100 mg. are about as effective as oral doses of 65 mg. of codeine. Lower doses, 32 mg., for example, are sometimes no more effective than a placebo, however.

Because of its relatively low activity, except at rather high doses, α, *d*-propoxyphene has been the subject of investigation, with the view of improving its effectiveness.

Miller, U.S. patent No. 3,845,192, patented October 29, 1974, reported that the addition of one or both of the tranquilizers chlordiazepoxide and diazepam to α, *d*-propoxyphene even at doses below those at which these benzodiazepines exhibit tranquilizing effects results in improved analgesia, notably a higher pain threshold. No other benzodiazepines are referred to.

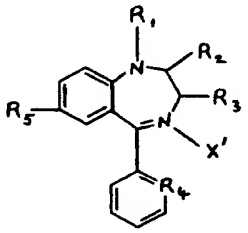
Miller, U.S. patent No. 3,749,797, patented July 31, 1973 suggested combinations of α, *d*-propoxyphene and namoxyrate, and No. 3,800,041 suggested combinations of α, *d*-propoxyphene and indomethacin, each of which give an enhanced analgesic effect.

In all of these combinations, at least one component, and in the case of the latter mentioned patent, both to the components, are analgesics.

In accordance with the invention of U.K.

Patent Number 1,538,160 mixtures of α, *d*-propoxyphene and/or α, *l*-propoxyphene with one or more of selected benzodiazepines display an enhanced analgesic activity, greater than that of α, *d*-propoxyphene or the benzodiazepine alone. That such mixtures have an enhanced analgesic activity is quite remarkable, in view of the lack of appreciable analgesic activity of the benzodiazepine component. While it might be expected that mixtures containing α, d-propoxyphene would have at least the analgesic activity of α, *d*-propoxyphene, it would not be expected that mixtures containing both the α, *d*-propoxyphene and benzodiazepine would have an enhanced analgesic activity, inasmuch as the benzodiazepines are not analgesics. Some of the benzodiazepines effective in the mixtures of the invention are in fact pharmaceologically inert, and are not even tranquilizers.

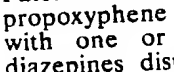
In the said U.K. Patent, the benzodiazepines of which at least one and optionally two, three or more are employed in admixture with α, *d*-propoxyphene and/or α, *l*-propoxyphene are defined by the formula:



In the above formula, R_1 is selected from hydrogen, alkyl, $—CH_2—\triangleleft$, and amino or alkylamino of the type

in which R and R′ are selected from hydrogen, lower alkyl having from one to three carbon atoms, bivalent alkylene having from two to four carbon atoms; and linked to the nitrogen at two positions to form a heterocyclic ring and diethylaminoethyl; provided when the propoxyphene is the α, *d*-isomer, R_1 is not alkyl:

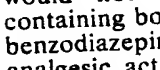
R_2 is selected from oxo oxygen =O hydroxyl OH, dihydroxyl, alkyl, and amino or alkylamino,



where R and R′ are as defined above, provided when the propoxyphene is the α, *d*-isomer, R_2 is =O, OH or $(OH)_2$.

R_3 is selected from hydrogen, hydroxyl OH and carboxyl COOH;

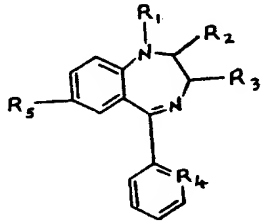
R_4 is selected from >CH, and >C—X, where X is halogen, and amino or alkylamino



where R and R′ are as defined above provided when the propoxyphene is the α, *d*-isomer, R_4 is >CH or >C—X where X is U or F;

R_5 is selected from hydrogen, halogen and nitro NO_2 provided when the propoxyphene is the α, *d*-isomer, R_5 is H, U or F; and X′ is a lone pair of electrons or an oxygen atom forming a co-ordinate bond with the nitrogen in the 4-position.

In accordance with the present invention, it has now been determined that additional benzodiazepines of similar structure can also be employed in admixture with α, *d*-propoxyphene. In these benzodiazepines which have the formula:



wherein

R_1 is hydrogen or methyl;

R_2 is hydrogen or oxo oxygen =O;

R_3 is hydrogen;

R_4 is >CH or >N; and

R_5 is NO_2, Cl or Br provided that when R_5 is U and R_1 is methyl then R_2 is other than oxo oxygen = O and that when R_1 and R_3 are both hydrogen, R_5 is NO_2 or Br.

Representative benzodiazepines falling within the above formula which can be employed include:

	R_1	R_2	R_3	R_4	R_5
Nitrazepam	H	=O	H	>CH	NO_2
Medazepam	CH_3	H	H	>CH	Cl
Bromazepam	H	=O	H	>N	Br

The α, *d*-propoxyphene and benzodiazepine can be employed as the free base or as their pharmaceutically acceptable salts. A pharmaceutically acceptable salt is a salt whose toxicity is not significantly greater than that of the free base. Pharmaceutically acceptable salts are readily prepared by reaction of the free amine with an organic or inorganic acid providing a pharmaceutically acceptable anion. Any pharmaceutically acceptable salt can be used including, for example, the hydrochloride, hydrobromide, sulphate, bisulphate, acetate, salicylate, valerate, oleate, phenate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, and napsylate. Usually, the *dextro*-propoxyphene is employed as the hydrochloride or napsylate salt, and the benzodiazepine is normally employed as the hydrochloride.

In the compositions of the invention, the α, *d*-propoxyphene gives an effective analgesic effect in a single oral dose providing an amount within the range from about 0.5 to about 30 mg propoxyphene per kg of animal body weight. The doses can, of course, be varied according to the species of animal being treated, the particular state which is treated, the route of administration, and other factors, as is well known. If the species is a sensitive one, a lesser oral dose will suffice, such as, for a single oral dose, an amount of propoxyphene within the range from 0.5 to about 5 mg per kg of animal body weight. In parenteral administration, the doses are lower by a factor of one-third to one-fifth of the amount of the oral doses. For medical applications, it is suggested that reference be made to *The Physician's Desk Reference to Pharmaceutical Specialties and Biologicals*, 27th Edition (1973) Medical Economics, Inc., page 875.

The benzodiazepine is used in an amount to impart an enhanced analgesic activity to the analgesic α, *d*-propoxyphene which amount accordingly constitutes a potentiating dose. The potentiating dose varies with the benzodiazepine, and also varies with the species of animal, the veterinary or medical state being treated, the route of administration, and other known factors.

Generally, an analgesic effect is obtained by employing any of the benzodiazepines in the normal dosage amounts for the particular benzodiazepine employed when used as a tranquilizer. The tranquilizing dosage amounts for benzodiazepines are set forth in *The Physician's Desk Reference of Pharmaceutical Specialties and Biologicals*, 27th Edition (1973), Medical Economics, Inc., pages 537, 1169, 1178 and 1567 or in similar publications such as *Martindale, The Extra Pharmacopoeia, The Pharmaceutical Press*, London, 26th Edition (1972). Lesser doses can, however, be used provided only that the relative proportions of benzodiazepine and propoxyphene in the compositions of the invention are selected to give an analgesic effect. The relative proportions depend, of course, upon the particular benzodiazepine employed, the animal, the veterinary or medical state being treated, the route of administration, and other known factors. In general, however, the weight ratio of propoxyphene:benzodiazepine is within the range from 100:5 to 2:1.

The compositions in accordance with the invention are nonaddictive, and consequently administration of the compositions can be repeated intermittently or recurringly, on a regular or irregular basis, as required.

The process in accordance with the invention accordingly comprises administering to a warm-blooded animal (i.e. a mammal) α, *d*-propoxyphene and a benzodiazepine, separately, i.e., in succession, or together, in amounts to give an analgesic effect when present together in the animal. In general, the compositions are conveniently administered and accordingly are usually formulated together with inert adjuvants appropriate for the particular composition and route of administration that is selected.

The preferred route of administration is orally. The compositions for oral administration can assume any of the normal forms, such as tablets, capsules, suspensions, elixirs, powders and jellies. The compositions can also be administered parenterally, such as by intramuscular, intravenous or subcutaneous administration, using conventional pro-

cedures, or in the form of rectal suppositories.

In admixture with adjuvants and inert diluents, the compositions of the invention can have any desired concentration of the active ingredients, i.e., the propoxyphene and benzodiazepine. A more concentrated composition can be formulated for dilution with water or other inert liquid before use. Usually, however, it is convenient to have the composition available in unit dose form, i.e., a unit dosage amount such that one portion of the composition provides the normally desired dose. Larger doses can be obtained by combining units, and lesser doses by subdividing units, facilitated by score lines or demarcations of somewhat conventional sort.

The compositions of the present invention can also include additional active ingredients to bolster or supplement the analgesic effect, including, for example, aspirin, acetylsalicylic acid, acetylphenetadine, acetylaminophene, codeine, and similarly analgesically active components.

In accordance with usual medical practice, the compositions in accordance with the present invention can be supplied in unit dose compositions comprising from about 25 to about 200 mg of the propoxyphene (calculated as the free base) and from about 0.5 to about 25 mg of the benzodiazepine or benzodiazepines (calculated as the free base), per dosage unit.

The compositions in accordance with the invention are evaluated using the standardized "hot plate" test for analgesia as described in U.K. patent No. 1,538,160 and by Nathan B. Eddy and Dorothy Lineback, *The Journal of Pharmacological and Experimental Therapy 107* 385 (1953). It is generally accepted that this test measures analgesic action and that the results obtained in this test are applicable to all kinds of warm-blooded animals including man. The results of the test can be extrapolated to humans in a relative or qualitative but not in a quantitative manner.

The test results show the potentiating effect of the benzodiazepines used in the compositions of the invention on the analgesic activity of Darvon (a commercially available *α-d*-propoxyphene), and that this effect is not correlated with other pharmacological activity or inactivity.

The following are Examples of compositions for dosage units or other application forms in accordance with the invention:

Tablet formulation

	Parts by weight/ tablet
Mixture of the present invention	15
Lactose	86
Corn starch (dried)	45.5
Gelatin	2.5
Magnesium stearate	1.0

The active compounds were powdered and passed through a sieve, and well mixed with the lactose and 30 mg of the corn starch.

The mixed powders were combined with a warm gelatin solution prepared by stirring the gelatin in water and heating to form a 10% w/w solution, then granulated by passing through a B.S. No. 12 sieve, and the moist granules were dried at 40°C.

The dried granules were re-granulated and the balance of the starch and the magnesium stearate were added and thoroughly mixed.

The granules were compressed to produce tablets each weighing 150 mg.

Tablet formulation

	Parts by weight/ tablet
Mixture of the present invention	100
Lactose	39
Cornstarch (dried)	80
Gelatin	4.0
Magnesium stearate	2.0

The method of preparation is identical with that of the preceding, except that 60 parts of starch is used in the granulation process and 20 parts during tableting.

Capsule formulation

	Parts by weight/ capsule
Mixture of the present invention	250
Lactose	150

The active compounds and lactose were passed through a sieve and the powders well mixed together before filling into hard gelatin capsules of suitable size, so that each capsule contained 400 mg of the mixture.

Suppositories

	Parts by weight/ suppository
Mixture of the present invention	50
Cocoa butter	950

The active compounds were powdered and passed through a sieve and triturated with molten cocoa butter at 45°C to form a smooth suspension.

The mixture was well stirred and poured into moulds, each of nominal 1 g capacity, to produce suppositories.

Cachets

	Parts by weight/ cachet
Mixture of the present invention	100
Lactose	400

The active compounds were passed through a sieve, then mixed with lactose previously sieved and filled into cachets of suitable size so that each contained 500 mg of the mixture.

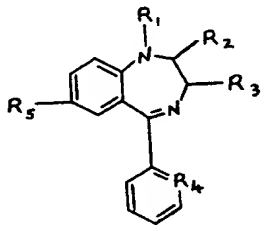
Intramuscular injection
(suspension in aqueous vehicle)

	Parts (by weight)
Mixture of the present invention	10
Sodium citrate	5.7
Sodium carboxymethyl-cellulose (low viscosity grade)	2.0
Methyl para-hydroxy-benzoate	1.5
Propyl para-hydroxy-benzoate	0.2
Water for injection to 1.0 ml.	

The sodium citrate and sodium carboxy-methylcellulose were mixed with sufficient water for injection at 90°C to effect dissolution. The mixture was cooled to 50°C and the methyl and propyl parahydroxy-benzoates were added, followed by the active compounds previously milled and sieved to 300 mesh. When cooled the injection was made up to volume and sterilized by heating in an autoclave.

WHAT I CLAIM IS:—

1. An analgesic composition comprising as analgesically active compounds α, *d*-propoxyphene or a pharmaceutically acceptable salt thereof and at least one benzodiazepine or a pharmaceutically accepted salt thereof in an amount which potentiates the analgesic activity of the propoxyphene compared to the analgesic activity of the propoxyphene above, the benzodiazepine having the formula:—



wherein:
R_1 is hydrogen or methyl;
R_2 is hydrogen or oxo oxygen =O;
R_3 is hydrogen;
R_4 is >CH, or >N; and
R_5 is NO_2, Cl and Br provided that when R_5 is Cl and R_1 is methyl then R_2 is other than oxo oxygen =O and that when R_1 and R_3 are both hydrogen R_5 is NO_2 or Br.

2. An analgesic composition in accordance with Claim 1 in which the benzodiazepine is one or more of nitrazepam, medazepam and bromazepam.

3. An analgesic composition in accordance with Claim 1 in which R_1 is hydrogen.

4. An analgesic composition in accordance with Claim 1 in which R_1 is CH_3.

5. An analgesic composition in accordance with Claim 1 in which R_2 is =O.

6. An analgesic composition in accordance with Claim 1 in which R_2 is H.

7. An analgesic composition in accordance with Claim 1 in which R_1 is hydrogen and R_2 is oxo oxygen =O.

8. An analgesic composition in accordance with Claim 1 in which R_4 is >N.

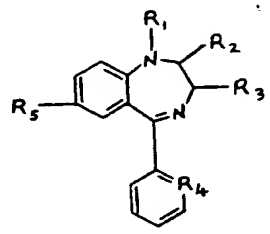
9. An analgesic composition in accordance with Claim 1 in which R_4 is >C—H.

10. An analgesic composition in accordance with Claim 1 in which R_5 is Cl.

11. An analgesic composition in accordance with Claim 1 in which R_5 is NO_2.

12. An analgesic composition in accordance with Claim 1 in which R_5 is Br.

13. A method of relieving pain in non-human mammals which comprises administering successively or together to the non-human mammal suffering from pain an analgesically effective amount α, d-propoxyphene or pharmaceutically acceptable salt thereof and at least one benzodiazepine or pharmaceutically acceptable salt thereof, the benzodiazepine having the formula:



wherein
R_1 is hydrogen or methyl;
R_2 is hydrogen or oxo oxygen =O;
R_3 is hydrogen;
R_4 is >CH or >N; and
R_5 is NO_2, Cl or Br provided that when R_5 is Cl and R_1 is methyl then R_2 is other than oxo oxygen =O and that when R_1 and R_3 are both hydrogen R_5 is NO_2 or Br.

14. A method in accordance with Claim 13 in which the benzodiazepine is one or more of nitrazepam, medazepam and bromazepam.

15. A pharmaceutical composition in dosage unit form comprising an analgesic composition in accordance with any of Claims 1 to 12 and a pharmaceutically acceptable carrier.

16. An analgesic composition as claimed in Claim 1 substantially as herein described with reference to the Examples.

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